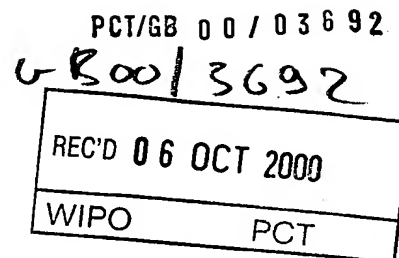


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Fee 170:-

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NOVEL COMPOUNDS

The present invention relates to certain thiazolopyrimidine compounds, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

EPA 778277 and WO 98/08847 each disclose a series of 6,5-hetero bicyclic compounds said to be useful as CRF antagonists.

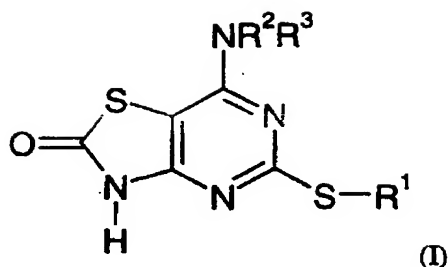
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

In accordance with the present invention, there is therefore provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



5 in which

R^1 represents a C_3 - C_7 carbocyclic, C_1 - C_8 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$ or an aryl or heteroaryl group, both of which may be
 10 optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^{10}$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^{10}$, C_1 - C_6 alkyl or trifluoromethyl groups;

R^2 and R^3 each independently represent a hydrogen atom, or a C_3 - C_7 carbocyclic,

15 C_1 - C_8 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

(a) halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^{10}$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^{10}$;

(b) a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^8 and itself optionally substituted by C_1 - C_3 -alkyl or halogen; or
 20

(c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-NR^8COR^{12}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1 - C_6 alkyl and trifluoromethyl groups;

25

R^4 represents hydrogen, C_1 - C_6 alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{11}$ and $-NR^{12}R^{13}$

R^5 and R^6 independently represent a hydrogen atom or a C_1 - C_6 alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{14}$ and $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$

5 or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally comprising a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, $-OR^{14}$, $-COOR^{14}$, $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$ or C_1 - C_6 alkyl, itself optionally substituted by one or more substituents independently selected from halogen atoms and $-NR^{15}R^{16}$ and $-OR^{17}$ groups;

15 R^{10} represents a hydrogen atom or a C_1 - C_6 -alkyl or a phenyl group, the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{17}$ and $-NR^{15}R^{16}$; and

each of R^7 , R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} independently represents a hydrogen atom or a C_1 - C_6 , alkyl, or a phenyl group.

20

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched. Aryl groups include phenyl and naphthyl. Heteroaryl groups include 5- or 6-membered aromatic rings containing one or more heteroatoms selected from N, S, O.

25

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

30

In formula (I) above, the group R^1 represents a C_3 - C_7 carbocyclic, C_1 - C_8 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$ or an aryl or heteroaryl group, both of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$,

35

-COOR⁷, -NR⁸COR¹⁰, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R¹⁰, C₁-C₆ alkyl or trifluoromethyl groups. Particularly advantageous compounds of formula (I) are those in which R¹ represents an optionally substituted benzyl group. More preferably R¹ represents benzyl or benzyl substituted by one or more halogen atoms, in particular benzyl substituted by two fluoro atoms.

Suitably R² and R³ each independently represent a hydrogen atom, or a C₃-C₇ carbocyclic, C₁-C₈ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

- (a) halogen atoms, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR¹⁰, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R¹⁰
- (b) a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR⁸ and itself optionally substituted by C₁-C₃-alkyl or halogen,
- (c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -NR⁸COR¹², -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆ alkyl and trifluoromethyl groups.

Preferably one of R² and R³ is hydrogen and the other is C₁-C₈ alkyl substituted by hydroxy and one or more methyl or ethyl groups. More preferably one of R² and R³ is hydrogen and the other is CH(CH₃)CH₂OH, CH(Et)CH₂OH or C(CH₃)₂CH₂OH.

Particularly preferred compounds of the invention include:

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(*R*)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(*R*)-7-[-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(*R*)-5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1-methylethyl)amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

and their pharmaceutically acceptable salts and solvates.

According to the invention there is also provided a process for the preparation of a compound of formula (I) which comprises:

treatment of a compound of formula (II):



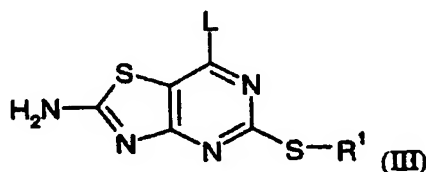
(II)

where R^1 , R^2 and R^3 are as defined in formula (I) and X is a leaving group with a metal alkoxide, followed by treatment with an acid or base and optionally forming a pharmaceutically acceptable salt.

X is any suitable leaving group such as halogen. The reaction may be carried out in an alcohol solvent such as methanol and the deprotection carried out in a solvent such as 1,4-dioxane. Examples of metal alkoxides include potassium methoxide. Examples of suitable acids include hydrochloric acid. Preferably the compound of formula (II) is treated with acid such as conc. HCl in a solvent such as 1,4-dioxane.

Compounds of formula (II) where R^1 , R^2 and R^3 are as defined in formula (I) and X is a halogen, may be prepared from corresponding compounds (II') where R^1 , R^2 and R^3 are as defined in formula (II) and X is NH_2 by treatment with a diazotizing agent such as isoamyl nitrite and a halogenating agent such as bromoform.

Compounds of formula (II') where R^1 , R^2 and R^3 are as defined in formula (II) and X is NH_2 may be prepared by treatment of a compound of formula (III):



where R^1 is as defined in formula (I) and L is a leaving group such as chlorine with an amine HNR^2R^3 where R^2 and R^3 are as defined in formula (I). The reaction may be carried out in a solvent such as *N*-methyl-pyrrolidine at a temperature between 0°C and 150°C .

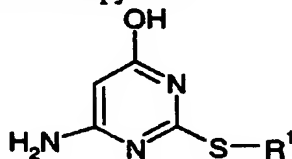
- 5 Compounds of formula (III) where R^1 is as defined in formula (I) and L is a halogen may be prepared by treating a compound of formula (III) where R^1 is as defined in formula (I) and L is a hydroxyl group with a halogenating agent such as phosphorous oxychloride. The reaction may be carried out in dimethylaniline at reflux.
- 10 Compounds of formula (III) where R^1 is as defined in formula (I) and L is a hydroxyl group may be formed by heating a compound of formula (IV) where R^1 is as defined above.



(IV)

The reaction is preferably carried out in a suitable solvent such as DMF at elevated temperature, for example at about 120°C .

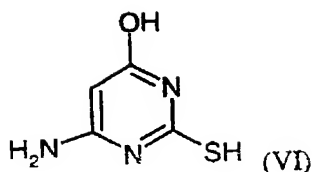
20 Compounds of formula (IV) may be readily prepared by reacting a compound of general formula (V) wherein R^1 is as defined above, with potassium thiocyanate and bromine in an inert solvent such as dimethylformamide/pyridine.



(V)

25 Compounds of formula (V) are suitably prepared by reacting a compound of formula (VI):

7



with a compound of formula R^1X where R^1 is as defined above and X is a leaving group such as bromide in the presence of a base such as sodium hydride in an inert solvent such as DMF at ambient temperature.

The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1991).

Novel intermediate compounds form a further aspect of the invention.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CXCR2) activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

- (1) (the respiratory tract) obstructive airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis;

sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

5 (2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

10 (3) **(skin)** psoriasis, atopic dermatitis, contact dermatitis and other eczematous dermatides, seborrhectic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

15 (4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

20 (5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, Sezary syndrome and idiopathic thrombocytopenia purpura;

25 (6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) cancers, especially non-small cell lung cancer (NSCLC) and squamous sarcoma;

30 (8) diseases in which angiogenesis is associated with raised CXCR2 chemokine levels (e.g. NSCLC); and

(9) cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and sepsis.

35 Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

5 In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

10 In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

15 The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a CXCR2 receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

20 The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

25 For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

30 The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, 35 still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

5 The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

10 The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form
15 of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The invention will now be further illustrated by reference to the following examples. In the examples the Nuclear Magnetic Resonance (NMR) spectra were measured on a Varian
20 Unity Inova 300 or 400 MHz spectrometer and the Mass Spectrometry (MS) spectra measured on a Finnigan Mat SSQ7000 or Micromass Platform spectrometer. Where necessary, the reactions were performed under an inert atmosphere of either nitrogen or argon. Chromatography was generally performed using Matrex Silica 60[®] (35-70 micron) or Prolabo Silica gel 60[®] (35-70 micron) suitable for flash silica gel chromatography.
25 High pressure liquid chromatography purification was performed using either a Waters Micromass LCZ with a Waters 600 pump controller, Waters 2487 detector and Gilson FC024 fraction collector or a Waters Delta Prep 4000. The abbreviations m.p. and DMSO used in the examples stand for melting point and dimethyl sulphoxide respectively.

Example 1

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

5 (a) **6-Amino-1,4-dihydro-2-[(phenylmethyl)thio]-4-oxo-5-thiocyanic acid, pyrimidinyl ester**

10 6-Amino-2-[(phenylmethyl)thio]-4(1*H*)-pyrimidinone (10.5g) [preparation as described in WO 9635678] and potassium thiocyanate (25g) in *N,N*-dimethylformamide (200ml) were heated together at 65°C. Pyridine (6.3ml) was added and the solution cooled to 5°C. Bromine (2.2ml) was added slowly and the reaction mixture stirred for 2 hours at 5-10°C. The reaction mixture was poured onto ice water, stirred for 1 hour and the solid was isolated by filtration. After washing with water and ether, a pure sample was obtained after
15 trituration with hot methanol.

MS (APCI) 291 (M+H, 100%).

(b) **2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7(4*H*)-one**

20 The product of step a) (7.35g) was heated at 120°C in *N,N*-dimethylformamide (40ml)/water (10ml) for 10 hours. After cooling, the resulting solid was filtered off, washed with water, then ethyl acetate to give the subtitle compound.

25 m.p. 325°C

MS (APCI) 291 (M+H, 100%).

(c) **7-Chloro-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2-amine**

30 The product from step b) (0.89g), phosphorus oxychloride (12ml) and *N,N*-dimethylaniline (1.2ml) were heated at reflux for 2 hours. The cooled reaction mixture was poured onto ice water and stirred for 2 hours. Chromatography (SiO₂, methanol/dichloromethane as eluant) gave the sub-title compound.

35 m.p. 217-218.5°C

MS (APCI) 309 (M+H, 100%).

(d) 2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol

5 The product from step c) (0.6g) and 1-amino-2-methyl-propan-2-ol (1.1g) in tetrahydrofuran (10ml) was heated in a sealed vessel at 100 °C for 18 hours. The mixture was evaporated to dryness and purified (SiO₂, ethyl acetate as eluant) to give the subtitle compound (0.46g).

10 MS (APCI) 362 (M+H⁺, 100%).

(e) 2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol

15 To a solution of the product from step d) (0.1g) in bromoform (5ml) was added isoamyl nitrite (0.13ml) and the mixture heated at 60°C for 10 mins. The mixture was evaporated to dryness and purified (SiO₂, ethyl acetate: dichloromethane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.043g).

20 MS (APCI) 427 (M+H⁺, 100%).

(f) 2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol

25 To a solution of the product from step e) (0.36g) in methanol (5ml) was added potassium hydroxide (0.095g) and the mixture stirred for 30 mins. The mixture was neutralised with concentrated hydrochloric acid then evaporated to dryness and purified (SiO₂, ethyl acetate: dichloromethane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.245g).

30 MS (APCI) 377 (M+H⁺, 100%).

(g) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]-thiazol [4,5-*d*]pyrimidin-2(3*H*)-one

To a solution of the product from step f) (0.21g) in 1,4-dioxane (5ml) was added water (0.1ml) and concentrated hydrochloric acid (1 drop). The mixture heated at 45°C for 3 hours then evaporated to dryness. Recrystallisation (acetonitrile) gave the title compound (0.110g).

MS (APCI) 363 ($M+H^+$, 100%).

NMR δ H (d_6 -DMSO) 12.37 (1H, s), 7.43-7.23 (5H, m), 6.61 (1H, s), 4.81 (1H, t), 4.34 (2H, s), 3.55 (2H, s), 1.32 (6H, s).

EXAMPLE 2

(*R*)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one
(a) (*R*)-2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-butanol

Prepared by the method of example 1 step d), using the product of example 1 step c) and (*R*)-(-)-2-amino-1-butanol.

MS (APCI) 362 ($M+H^+$, 100%).

(b) (*R*)-2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-butanol

Prepared by the method of example 1 step e), using the product of example 2 step a).

MS (APCI) 427 ($M+H^+$, 100%).

(c) (*R*)-2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-butanol

Prepared by the method of example 1 step f), using the product of example 2 step b).

MS (APCI) 377 ($M+H^+$, 100%).

5 (d) (*R*)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-
d]pyrimidin-2(3*H*)-one

Prepared by the method of example 1 step g), using the product of example 2 step c).

MS (APCI) 363 ($M+H^+$, 100%).

10 NMR δ H (d_6 -DMSO) 12.37 (1H, s), 7.43-7.21 (6H, m), 4.67 (1H, t), 4.31 (2H, s), 4.09
(1H, s), 3.47-3.32 (2H, m), 1.69-1.59 (1H, m), 1.48-1.41 (1H, m), 0.82 (3H, t).

EXAMPLE 3

15 (*R*)-7-[-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-
d]pyrimidin-2(3*H*)-one

(a) (*R*)-2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1-
propanol

20 Prepared by the method of example 1 step d), using the product of example 1 step c) and
(*R*)-(-)-2-amino-1-propanol.

MS (APCI) 412 ($M+H^+$, 100%).

25 (b) (*R*)-2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1-
propanol

Prepared by the method of example 1 step e), using the product of step a)

30 MS (APCI) 348 ($M+H^+$, 100%).

(c) (*R*)-2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1-
propanol

35 Prepared by the method of example 1 step f), using the product of step b)

MS (APCI) 363 ($M+H^+$, 100%).

(d) (R)-7-[-2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-
d]pyrimidin-2(3H)-one

Prepared by the method of example 1 step g), using the product of example 3 step c).

MS (APCI) 349 ($M+H^+$, 100%).

NMR δ H (d_6 -DMSO) 12.38 (1H, s), 7.44-7.20 (6H, m), 4.73 (1H, t), 4.32 (2H, m), 4.23 (1H, m), 3.49-3.31 (2H, m), 1.12 (3H, d).

EXAMPLE 4

5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]-
thiazolo[4,5-d]pyrimidin-2(3H)-one

(a) 2-Amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7(3H)-one

Potassium *t*-butoxide solution (0.45ml of 1M solution in tetrahydrofuran) was added to a stirred solution of 2-amino-5,6-dihydro-5-thioxo-thiazolo[4,5-d]pyrimidin-7(4H)-one (0.09g) [Cited: Indian J. Chem., Sect. B (1989), 28B(11), 964-5.] and 2,3-difluorobenzyl bromide in dimethyl sulphoxide (2ml). After stirring for 3 days, the reaction mixture was poured onto water to give and the subtitle compound, isolated by filtration.

MS (APCI) 327 ($M+H^+$, 100%).

(a) 7-Chloro-5-[[[(2,3-difluorophenyl)methyl]thio]-thiazolo[4,5-d]pyrimidin-2-amine

Prepared by the method of example 1 step c), using the product of step a).

MS (APCI) 345 ($M+H^+$, 100%).

(b) 2-[[2-Amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazol [4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol

Prepared by the method of example 1 step d), using the product of example 4, step b) and
5 2-amino-2-methylpropanol.

MS (APCI) 398 (M+H⁺, 100%).

(c) 2-[[2-Bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol

Prepared by the method of example 1 step e), using the product of step c).

MS (APCI) 462 (M+H⁺, 100%).

(d) 2-[[5-[[[(2,3-Difluorophenyl)methyl]thio]-2-methoxy-thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol

Prepared by the method of example 1 step f), using the product of step d).

MS (APCI) 413 (M+H⁺, 100%).

(e) 5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

Prepared by the method of example 1 step f), using the product of example 4 step d).

MS (APCI) 399 (M+H⁺, 100%).

NMR δ H (*d*₆-DMSO) 12.41 (1H, s), 7.41-7.30 (2H, m), 7.21-7.13 (1H, m), 6.64 (1H, s),
25 4.79 (1H, t), 4.41 (2H, s), 3.53 (2H, d), 1.29 (6H, s).

EXAMPLE 5

(*R*)-5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1-methylethyl)amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) (*R*)-2-[[2-Amino-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

Prepared by the method of example 1 step d), using the product of example 4 step b) and (R)-(-)-2-amino-1-propanol.

5 MS (APCI) 384 ($M+H^+$, 100%).

(b) (R)-2-[[2-Bromo-5-[[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

10 Prepared by the method of example 1 step e), using the product of step a).

MS (APCI) 448 ($M+H^+$, 100%).

15 (a) (R)-2-[[5-[[[(2,3-difluorophenyl)methyl]thio]-2-methoxy-thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

Prepared by the method of example 1 step f), using the product of step b)

MS (APCI) 398 ($M+H^+$, 100%).

20 (d) (R)-5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1-methylethyl)amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

Prepared by the method of example 1 step g), using the product of step c).

25 MS (APCI) 385 ($M+H^+$, 100%).

NMR δ H (d_6 -DMSO) 12.41 (1H, s), 7.41-7.11 (6H, m), 4.72 (1H, t), 4.39 (2H, m), 4.23 (1H, m), 3.47-3.29 (2H, m), 1.10 (3H, d).

30

Pharmacological Data

Ligand Binding Assay

35 [125 I]IL-8 (human, recombinant) was purchased from Amersham, U.K. with a specific activity of 2,000Ci/mmol. All other chemicals were of analytical grade. High levels of hrCXCR2 were expressed in HEK 293 cells (human embryo kidney 293 cells ECACC No.

85120602) (Lee *et al.* (1992) *J. Biol. Chem.* 267 pp16283-16291). hrCXCR2 cDNA was amplified and cloned from human neutrophil mRNA. The DNA was cloned into PCRScript (Stratagene) and clones were identified using DNA. The coding sequence was sub-cloned into the eukaryotic expression vector RccMV (Invitrogen). Plasmid DNA was prepared using Quiagen Megaprep 2500 and transfected into HEK 293 cells using Lipofectamine reagent (Gibco BRL). Cells of the highest expressing clone were harvested in phosphate-buffered saline containing 0.2%(w/v) ethylenediaminetetraacetic acid (EDTA) and centrifuged (200g, 5min.). The cell pellet was resuspended in ice cold homogenisation buffer [10mM HEPES (pH 7.4), 1mM dithiothreitol, 1mM EDTA and a panel of protease inhibitors (1mM phenyl methyl sulphonyl fluoride, 2µg/ml soybean trypsin inhibitor, 3mM benzamidine, 0.5µg/ml leupeptin and 100µg/ml bacitracin)] and the cells left to swell for 10 minutes. The cell preparation was disrupted using a hand held glass mortar/PTFE pestle homogeniser and cell membranes harvested by centrifugation (45 minutes, 100,000g, 4°C). The membrane preparation was stored at -70°C in homogenisation buffer supplemented with Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH₂PO₄), 0.1%(w/v) gelatin and 10%(v/v) glycerol.

All assays were performed in a 96-well MultiScreen 0.45µm filtration plates (Millipore, U.K.). Each assay contained ~50pM [¹²⁵I]IL-8 and membranes (equivalent to ~200,000 cells) in assay buffer [Tyrode's salt solution supplemented with 10mM HEPES (pH 7.4), 1.8mM CaCl₂, 1mM MgCl₂, 0.125mg/ml bacitracin and 0.1%(w/v) gelatin]. In addition, a compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to reach a final concentration of 1%(v/v) DMSO. The assay was initiated with the addition of membranes and after 1.5 hours at room temperature the membranes were harvested by filtration using a Millipore MultiScreen vacuum manifold and washed twice with assay buffer (without bacitracin). The backing plate was removed from the MultiScreen plate assembly, the filters dried at room temperature, punched out and then counted on a Cobra γ-counter.

The compounds of formula (I) according to the Examples were found to have IC₅₀ values of less than (<) 10µM.

Intracellular Calcium Mobilisation Assay

Human neutrophils were prepared from EDTA-treated peripheral blood, as previously described (Baly *et al.* (1997) *Methods in Enzymology* 287 pp70-72), in storage buffer

[Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH₂PO₄) supplemented with 5.7mM glucose and 10mM HEPES (pH 7.4)].

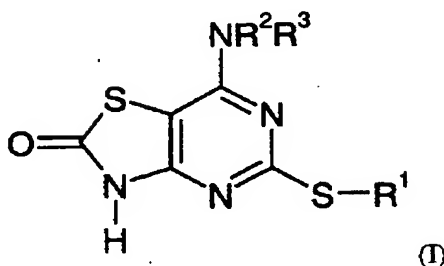
5 The chemokine GRO α (human, recombinant) was purchased from R&D Systems (Abingdon, U.K.). All other chemicals were of analytical grade. Changes in intracellular free calcium were measured fluorometrically by loading neutrophils with the calcium sensitive fluorescent dye, fluo-3, as described previously (Merritt *et al.* (1990) *Biochem. J.* 269, pp513-519). Cells were loaded for 1 hour at 37°C in loading buffer (storage buffer with 0.1%(w/v) gelatin) containing 5 μ M fluo-3 AM ester, washed with loading buffer and
10 then resuspended in Tyrode's salt solution supplemented with 5.7mM glucose, 0.1%(w/v) bovine serum albumin (BSA), 1.8mM CaCl₂ and 1mM MgCl₂. The cells were pipetted into black walled, clear bottom, 96 well micro plates (Costar, Boston, U.S.A.) and centrifuged (200g, 5 minutes, room temperature).

15 A compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A₅₀ concentration of GRO α and the transient increase in fluo-3 fluorescence (λ_{ex} = 490nm and λ_{em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

20 The compounds of formula (I) according to the Examples were tested and found to be antagonists of the CXCR2 receptor in human neutrophils.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



in which

- R^1 represents a C_3 - C_7 carbocyclic, C_1 - C_8 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$ or an aryl or heteroaryl group, both of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^{10}$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^{10}$, C_1 - C_6 alkyl or trifluoromethyl groups;

R^2 and R^3 each independently represent a hydrogen atom, or a C_3 - C_7 carbocyclic, C_1 - C_8 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

- (a) halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^{10}$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^{10}$
- (b) a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR⁸ and itself optionally substituted by C_1 - C_3 -alkyl or halogen,
- (c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-NR^8COR^{12}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1 - C_6 alkyl and trifluoromethyl groups;

R⁴ represents hydrogen, C₁-C₆ alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹¹ and -NR¹²R¹³

- 5 R⁵ and R⁶ independently represent a hydrogen atom or a C₁-C₆ alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹⁴ and -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶
- or
- 10 R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally comprising a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, -OR¹⁴, -COOR¹⁴, -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶ or C₁-C₆ alkyl, itself
- 15 optionally substituted by one or more substituents independently selected from halogen atoms and -NR¹⁵R¹⁶ and -OR¹⁷ groups;

- R¹⁰ represents a hydrogen atom or a C₁-C₆-alkyl or a phenyl group, the latter two of which may be optionally substituted by one or more substituent groups independently selected
- 20 from halogen atoms, phenyl, -OR¹⁷ and -NR¹⁵R¹⁶; and

each of R⁷, R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ independently represents a hydrogen atom or a C₁-C₆, alkyl, or a phenyl group.

- 25 2. A compound according to claim 1, wherein R¹ represents an optionally substituted benzyl group.

3. A compound according to claim 1 or claim 2, wherein one of R² and R³ is hydrogen and the other is C₁-C₈ alkyl substituted by hydroxy and one or more methyl or ethyl groups.

- 30 4. A compound according to claim 1 selected from:

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-d]pyrimidin-2(3H)-one,

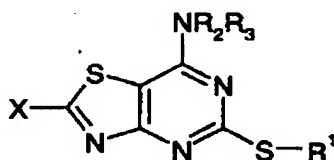
- (R)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]-thiazolo[4,5-d]pyrimidin-2(3H)-one,
- 35

(*R*)-7-[-2-Hydroxy-1-methylethylamino]-5-[(phenylmethyl)thio]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

- 5 (*R*)-5-[[[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1-methylethyl)amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
and their pharmaceutically acceptable salts and solvates.

5. A process for the preparation of a compound of formula (I) as defined in claim 1 which
10 comprises:
treatment of a compound of formula (II):



(II)

- 15 where R^1 , R^2 and R^3 are as defined in formula (I) and X is a leaving group with a metal alkoxide, followed by treatment using an acid or base and optionally forming a pharmaceutically acceptable salt..

- 20 6. An intermediate compound of formula (II) as defined in claim 5.

7. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

- 25 8. A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 with a pharmaceutically acceptable adjuvant, diluent or carrier.

- 30 9. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 for use in therapy.

10. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 in the manufacture of a medicament for use in therapy.

5 11. A method of treating a chemokine mediated disease wherein the chemokine binds to a CXCR2 receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4.

10 12. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4.

15 13. A method according to claim 12, wherein the disease is psoriasis.

ABSTRACT

The invention provides certain thiazolopyrimidine compounds, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in
5 therapy.

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